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Study of X-Linked Mental Retardation (XLMR): Summary of 61 Families in the Miami/Greenwood Study

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The initial goal of this study was to localize as many genes as possible that lead to syndromic and non-specific XLMR. More recently, this goal has been redefined to include narrowing these localizations and cloning specific genes. In the last 5 years, 61 families have participated in this study; 34 have a projected or actual lod score greater than 2.0. Restudy of 12 families reported previously has been a particularly productive aspect of this study and has led to clinical redefinition and new or improved localization of most of these syndromes. Five possible new XLMR syndromes have been identified. Five large families with non-specific XLMR have been regionally localized. Since many XLMR conditions are based on only 1 or 2 family reports, one of the major purposes of this summary is to provide clinical data on the study families so that collaborative projects can be undertaken with other centers that have similar families.

KEY WORDS: X-linked mental retardation, linkage, XLMR syndrome

INTRODUCTION

More than 100 XLMR syndromes and at least 41 families with non-specific XLMR are now known [Lubs et al., 1996]. Seventeen of the specific disorders have been cloned and in 33 the gene has been regionally mapped. The families with non-specific XLMR span 8–10 regionally distinct localizations [Gedeon et al., 1996; Lubs et al., 1996]. However, the clinical and linkage information in most of these disorders consists of data from only one or two families which makes the identification of additional families with each disorder important. The purpose of the present report is to summarize progress to date, and to present information about families that are still under study in the hope that similar families known to other investigators or families with overlapping localizations may be studied collaboratively.

METHODS

Ascertainment of Families

Most families were referred from other genetic centers in the United States, Canada and Europe. A particularly valuable set of families includes those whose clinical findings were reported over the past 40 years. A special effort was made to include these families in the study.

Families with at least ten potentially informative meioses and smaller families with a clear clinical diagnosis were admitted to the studies since their linkage data could be pooled with data from other families. The same criteria were employed for large families with respect to non-specific XLMR. Some smaller families were also included for exclusion mapping and for future testing for mutations in candidate genes.

Clinical Studies

Clinical evaluations of affected and non-affected relatives were carried out by a member of the study team and supplemented as appropriate by other specialists. The clinical protocol included a detailed genetic history of three or more generations, physical examination with attention to minor anomalies, gross anomalies, and anthropometric measurements [Schwartz, 1993]. Photographs were used to document abnormalities and psychometric studies quantified cognitive function. At least one affected member of each kindred had prometaphase chromosome analysis, plasma amino acid analysis, and FMR1 molecular analysis. Other laboratory studies and procedures (muscle biopsy, MRI, electromyography, electroencephalography, and serum chemistries) were performed at the discretion of the examiner.

Molecular Linkage Studies

The specific markers used for the linkage analysis have changed over this 5-year-period of the study and

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TABLE I. Current X Chromosome Markers for Analysis of Families With XLMR

Marker	Marker analysis	
	Location	Allele size
DXS996	Xp22.3	153–171
KAL	Xp22.3	179–187
DXS987	Xp21	206–224
DXS451	Xp21.2-22.3	182–204
DXS992	Xp21	201–211
DXS989	Xp21	173–199
DXS1110	Xp21	252–268
DXS993	Xp11.4	292–312
MAOA	Xp11.3	112–126
DXS1003	Xp11	169–195
DXS991	Xp11.21	266–290
AR	Xq13	261–312
DXS983	Xq13	173–183
DXS986	Xq13	149–173
DXS566	Xq13	211–219
DXS995	Xq21.1	193–199
DXS990	Xq21	172–180
DXS1002	Xq21.3	266–274
DXS101	Xq21.3-22	185–230
DXS1001	Xq24	197–215
DXS424	Xq24	126–142
DXS425	Xq25	90–110
HPRT	Xq26	263–299
DXS984	Xq27.1	154–184
DXS548	Xq27.3	192–208
DXS1108	Xq28	163–177
DXS1113	Xq28	154–178

increased in number as more informative PCR-based markers have become available. The current screening panel consists of 26 microsatellite markers which provides coverage at an average distance of about 10 cM (Table I). The markers are run in six groups through each family providing a standard data set for all families. Appropriate references to these markers can be found in Willard et al. [1994]. Linkage analysis was carried out using MLINK V5.1 [Lathrop and Lalouel, 1984]. Multipoint analysis was conducted using LINKMAP V5.1 [Lathrop et al., 1985].

Computer Database for XLMR Syndrome

In addition to the clinical diagnosis, a computer database for XLMR syndromes, which was described previously [Arena and Lubs, 1991], was utilized in effecting diagnoses and in identifying possible new syndromes. This database was updated and revised since the initial publication to provide better searches and regionally based input and output. It is tentatively planned to make this system available through the Internet. In the interim, it can be utilized by providing appropriate photographs and clinical information to the authors at the University of Miami or University of Tromsø.

RESULTS

Sixty-one families were entered into the study; 42 had specific clinical findings (Tables II, III, and IV) and 19 had non-specific MR. Thirty-four were large families with a projected or actual lod score greater than 2.0.

Published Reports

The present study resulted in publication of new or improved regional localization for six XLMR syndromes (Table II). In some instances this was carried out within the study, in others through collaboration (Mohr-Tranebjaerg syndrome), and in still others by contributing families to studies in which cloning of a specific gene was being carried out (Aarskog-Scott syndrome).

Allan et al. reported the first XLMR syndrome in 1944. Restudy of this family (just prior to the beginning of this study) confirmed most of the original findings and resulted in localization of the gene to Xq21 [Stevenson et al., 1990; Schwartz et al., 1990]. Publication of these findings led to the referral of two similar families with hypotonia, contractions, and muscle atrophy and both have shown comparable localizations. However, possible facial abnormalities, which presented in the original family, were not present in either of these two families [Bialer et al., 1992; Schwartz et al., unpublished data] emphasizing the need to have data from several families for a definitive description of the phenotype.

Arena et al. [1992] reported on a family in which affected males were non-ambulatory and had minimal speech, titubation, spastic paraplegia, and ataxia. The combination of the extremely early onset, paraplegia, and spasticity of the lower limbs with sparing of the upper limbs, increased iron deposits in the basal ganglia at an early age, and probable localization to Xq22-q26

TABLE II. Published Localization Data

Disorder/syndrome	No. fam.	Study results		References
		Chromosome band	Limiting markers	
Allan-Herndon-Dudley MIM#309600	3	Xp11.4-q21.3	DXS106-DXYSI	Bialer et al., 1992
Arena MIM#	1	Xq22-q26	DXS3-DXS425	Arena et al., 1992
MASA Syndrome MIM#303350	6	Xq28	DXS304-DXS952	Boyd et al., 1993
Aarskog-Scott MIM#305400	8	Xp11.22	DXS1003-DXS566	Stevenson et al., 1994
Mohr-Tranebjaerg MIM#304700	1	Xq22	DXS990-DXS456	Tranebjaerg et al., 1995
Snyder-Robinson MIM#309583	1	Xp22.3-p21.3	DXS43-3′DMD	Arena et al., 1996

TABLE III. Original Families With XLMR Syndromes Included in Study

Fam. No.—Disorder MIM #	Clinical manifestations
8005—Allan-Herndon-Dudley[a] MIM#309600	Hypotonia, contractures, muscle atrophy
8045—Arena	Severe spastic paraplegia, ataxia, titubation
8070—Miles-Carpenter[b] MIM#309605	Exotropia, microcephaly, distal muscle wasting, low fingertip arches [Miles and Carpenter, 1991]
8075—Wieacker-Wolf[b] MIM#314580	Contractures, distal muscle atrophy, dyspraxia of ocular, and facial musc. [Wieacker et al., 1987]
8110—Renpenning[a] MIM#309500	Small head, testes, and stature
8145—Snyder-Robinson[a] MIM#309583	Thin, with muscle hypoplasia, osteoporosis and kyphoscoliosis
8160—Mohr-Tranebjaerg[a] MIM#304700	Progressive deafness, blindness, dementia, dystonia
8165—Apraxia and ataxia[b]	Ataxia, apraxia, seizures, tremor, club feet [Tranebjaerg et al., 1992]
8180—MR with psoriasis[b] MIM#309480	Seizures and psoriasis [Tranebjaerg et al., 1988]
8250—Aarskog-Scott[a] MIM#305400	Hypertelorism, down slanting eyes, anteverted nostrils, shawl scrotum
8275—Golabi-Ito-Hall[a] MIM#309530	Marked small stature, prom. ears, hypertelorism, microcephaly
8295—Lujan[a] MIM#309520	Thin, muscle hypoplasia, very high, narrow palate, hypernasal voice, and kyphoscoliosis

[a] Clinical restudy of original family.
[b] DNA from original family available (no clinical studies).

separated this disorder from other forms of X-linked spastic paraplegia. A second family with this new disorder has not been ascertained or reported.

In family 8200, with the MASA syndrome, the spectrum of this disorder was extended to include agenesis of the corpus callosum [Boyd et al., 1993]. The family was also included in a study of L1CAM mutations and was subsequently shown to have a missense H191Q alteration in the Ig2 domain [Vits et al., 1994; Jouet et al., 1994].

Aarskog described a family with an X-linked condition characterized by growth impairment and distinct craniofacial, musculoskeletal, and genital abnormalities at the 1970 conference on the Clinical Delineation of Birth Defects. Scott [1971] described a second family with nine affected males at the same conference. The family reported by Scott was restudied (Family 8250) and localization of the gene was found to be in the pericentric region of the X chromosome with multipoint analysis suggesting the locus to be on Xp [Stevenson et al., 1994]. Collaboration with other investigators who cloned a candidate gene resulted in documentation of the first mutation [Pasteris et al., 1994] in another family (8060) in our study. In a related study, 17 families, including the family reported by Aarskog, are currently undergoing mutation analysis.

In the family reported by Tranebjaerg et al. [1995], originally described by Mohr et al. [1960] as X-linked deafness (DFN1), a much more severe and widespread disorder including blindness, dystonia, progressive dementia, and deafness were found, again emphasizing the value of restudying families. The disorder was localized to Xq22.

The family reported by Snyder and Robinson in 1969 as non-specific XLMR was restudied by Arena et al. [1996] and was found to have developed a characteristic set of clinical findings. These included an extremely thin habitus with muscle hypoplasia, osteoporosis and kyphoscoliosis, facial asymmetry and a relatively prominent lower lip with thin upper lip, long hands with hyperextensible fingers, and long great toes. The disorder localized distal to DMD. This family illustrated the pitfalls in classifying a family as either nonspecific or as a syndrome and emphasizes the need to follow and restudy all XLMR families who do not have a clear diagnosis.

Families With Specific Disorders Under Study

Other families with syndromic XLMR still being investigated are shown in Table III. These include clinical reevaluation of the originally reported families with Renpenning, Golabi-Ito-Hall and Lujan syndromes.

The family with XLMR reported by Renpenning et al. [1962] was restudied extensively. The complexity of the current clinical findings, which suggest that two XLMR disorders may be segregating in the same family, has delayed completion of the linkage studies. However, the clinical findings in most relatives were not greatly changed from the original report. Other technical fac-

TABLE IV. Other Families With XLMR Syndromes Currently Under Study (Unpublished)

Family number	Clinical findings
8000	Four affected males in three generations; small head size
8010[a]	Ten affected males in two generations; macrocephaly, macroorchidism, severe MR, midface hypoplasia and triangular face
8030	Five affected males in three generations; hypotonia, hyporeflexia, tongue fasciculations, blindness, deafness, death by 1 year
8055[a]	Ten affected males in three generations; micrognathia, large ears, hypoplasia of two distal phalanges, absence of distal flexor creases
8140	Two affected brothers; macrocephaly, moderate MR, seizures, Angelman-like affect
8185	Two affected males in one generation; short stature, macrocephaly, coarse facial appearance
8195	Four affected males in two generations; dysarthria, ataxia, seizures, uncoordinated gait
8210[a]	Five affected males in one generation; dysphagia, respiratory infections, muscle hypoplasia, hypotonia and frontal bossing
8240[a]	Nine affected males in two generations; sloped forehead, small head size, short stature, small testicular volume
8300	Six affected males in three generations; profound MR, nonambulatory, URI, death at an early age
8355	Eight affected males in one generation; seizures, aphasia, ataxia, autism
8365	Two affected males and two affected females in three generations; overgrowth, hypertelorism, mild-moderate MR, macrocephaly, enamel hypoplasia, large ears and hands, tapered digits, clinodactyly 4th and 5th fingers, malimplanted toes
8395	Two affected brothers; spastic paraplegia, female carrier has gradual onset of gait problems and clonus in 4th decade
8435	Four affected males in four generations; seizures, large head, IgA deficiency, moderate MR, hypertelorism, synophrys
8440	Five affected males in two generations; mild MR, long 5th fingers, high palate, acanthosis nigricans

[a] Possible new disorder.

tors, including successful use of DNA from autopsy specimens in this family also have delayed completion of the linkage analysis.

The family originally reported by Golabi et al. in 1984 was restudied. Since the present lod score is less than 2, publication awaits completion of studies in a few additional relatives. The clinical findings were similar to the original report, but the degree of growth retardation was much more striking; the height of the index case at age 23 was only 1.5 m. DNA from two other small families (Table III) was provided to the study for exclusion mapping. We are waiting for the possible identification of similar families for additional studies that might assist in narrowing their localizations before completing their studies.

The family reported by Lujan et al. in 1985 as XLMR with a marfanoid habitus was restudied with confirmation of some clinical findings and significant changes in others. The marfanoid habitus was much less evident 10 years later, because of additional growth, and increased muscle mass and body fat. It seems likely that at least part of the "marfanoid" habitus reflected their adolescent status and that it is not one of the major findings of this XLMR syndrome. However, the very high arched palate, hypernasal speech, and high nasal bridge were found again. Since the family size and the current resulting lod scores are marginal, resolution of the localization of this disorder is awaiting collaborative studies with other centers having families with a comparable phenotype. Unfortunately, no large family is known to any of the centers interested in XLMR. Thus, resolution of the diagnosis (or diagnoses) for thin, tall males with minimal muscle mass and some marfanoid signs may take some time and may be difficult.

Possible New Disorders

Four possible new syndromes were identified from families referred to us for study (Table IV). These are either in the process of publication or further study at this time. Patients in family 8010 had macrocephaly, macroorchidism, severe MR, midface hypoplasia, and triangular face. Patients in family 8055 had a set of findings not known to us to occur in any other disorder, including micrognathia, large ears, and hypoplasia of the two distal phalanges. Patients in family 8210 have the unusual clinical findings of dysphagia, recurrent respiratory infections, hypotonia, and frontal bossing. Patients in family 8240 had findings similar to the orig-

inal Renpenning family, including small head size, small stature, and small testes, but the preliminary linkage studies suggested a different localization from that in the original Renpenning family [Schwartz et al., 1994]. Thus, it is likely that this phenotype results from mutations in more than one gene. Since the principal clinical findings (small head size, small stature, and small testes) in this syndrome are not unusual, this is not an unexpected result.

In family 8030, 5 males died at an early age (most in the first few months of life). In addition there was hypotonia, hyporeflexia, tongue fasciculation, and blindness. Unfortunately, we have only one available DNA specimen for testing. Similarly, in family 8300, six males with profound mental retardation died in the first months of life. The early clinical descriptions and localizations of disorders with early death and XLMR are currently incomplete and resolution of this group of disorders awaits the results of candidate gene and other testing.

A number of the families described in Table IV are small and linkage studies have been deferred awaiting the identification of a second similar family. Exclusion mapping is planned in the interim.

Non-Specific XLMR

Linkage studies in five families with non-specific XLMR having a lod score over 2 were completed (MRX 8, 29, 32 and two unpublished families, Table V). In addition, five large families and nine smaller families are in the process of linkage studies and exclusion mapping.

Computer Database

By using the computer database developed as part of this study, one can very easily display the upper and lower limits to the process of "lumping" and "splitting" for certain groups of syndromes. For example, 26 syndromes are described with short stature. Even though only 11 of these disorders have been localized, review of the computer database of the available 11 localizations (Fig. 1) suggests that as few as 3 loci might explain this set of disorders. Each might also be unique. Other uses of this database are described in the next section.

DISCUSSION

The first reported family in 6 of the 57 recessive XLMR syndromes [Lubs et al., 1996] was restudied (Table III-Renpenning, Snyder-Robinson, Mohr-Tranebjaerg, Aarskog-Scott, Golabi-Ito-Hall, Lujan). Many of the early reports contained only minimal information. The current restudy enabled 10–30 additional years of growth and development to be described with better clinical observations and photographs. Where the families were sufficiently large, regional localization was accomplished. This approach provides a firm base-line against which similar families can be compared in the future. Without such a deliberate and organized approach to this group of disorders, many questions about older reports will remain, and a completely satisfactory clinical and laboratory diagnostic approach to XLMR will not be possible. As described in the previous section, in nearly every instance important new clinical information was obtained.

It is likely that many of the currently reported 105 XLMR disorders are allelic and this process of reevaluation is critical in reaching an understanding of XLMR. Even when families are small, exclusion mapping may still provide data for comparison with other similar families and serve as a basis for efficient testing of candidate genes in clinically similar families.

The computerized data set for XLMR disorders, which was updated since the several reports 5 years ago [Arena and Lubs, 1991], has been useful as a means of comparing clinical findings in known entities with a study family and as a first step in considering whether the family has a new syndrome or not. It is also increasingly useful as an initial means of determining disorders that might be allelic. The limitations of the current system is that the line designating the localizations in Figure 1 are approximated from the molecular data onto the bands. Thus, they are not accurate at the locus level and if there is doubt about an overlapping localization, the primary literature must be consulted.

A number of benefits can result from information exchange among investigators in this field. Often family studies take a number of years to complete, because of changing technical factors, relatives who promise to cooperate, but do not become available for several years, delays in obtaining tissue from relatives that have died, etc. The finding of a borderline lod score also delays publication in the hope of finding additional relatives who might contribute to the lod score. Thus, it becomes important, for each group to be aware of families that are under study elsewhere so that the possibility of pooling linkage information can be considered

TABLE V. Non-Specific XLMR

	Linkage		Limiting markers	Reference
MRX8	Z = 2.36 Multipoint DXS326	θ = 0 (Xq21)	MAOA-DXS454	Schwartz et al., 1992
MRX29	Z = 3.31 DXS1202	θ = 0 (Xp21)	DXS989-DXS1068	Hane et al., 1996
MRX32	Z = 4.21 STR45	θ = 0 (Xp21)	DXS1053-DXS1110	In preparation
8035	Z = 2.5 DXS995	θ = 0 (Xq13)	DXS1162-DXS326	In preparation
8135	Z = 2.4 DXS425	θ = 0 (Xq22-q26)	DXS101-HPRT	In preparation

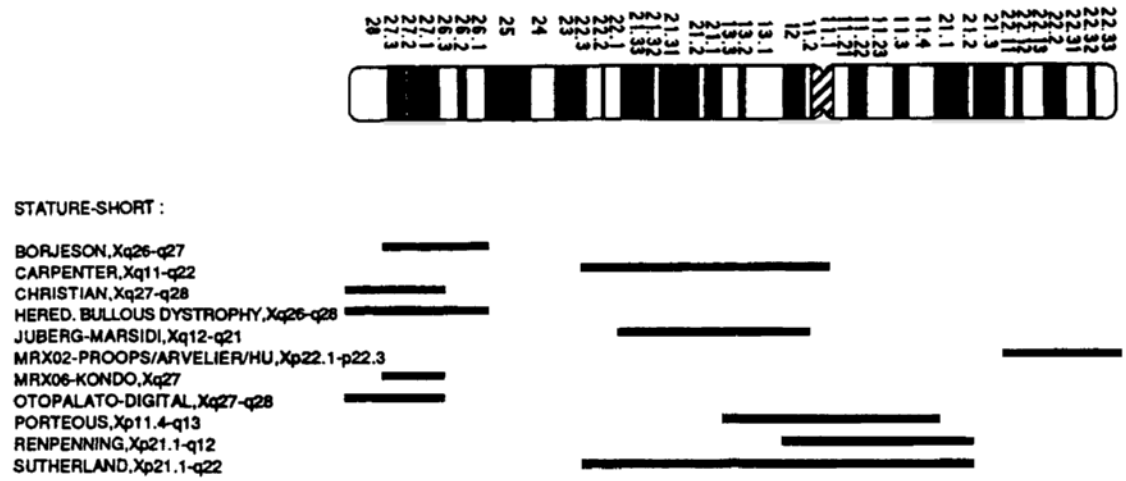

Fig. 1. Computer output of localizations of disorders with short stature. Three loci might account for these eleven disorders.

before publication. To bring this about, a formal collaborative database of XLMR families is needed. In addition, utilization of the computer diagnostic system may also be of help in this process and it is tentatively planned to make this system available through the Internet in 1996.

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